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Dear Drs Cox, Egerton, Braet and Members of the Editorial Board, *Micron*

## Call for Retraction: Howell RW, Bishayee A. Bystander effects caused by nonuniform distributions of DNA-incorporated $^{125}$I. *Micron* 33: 127-133 (2002)

**We have analyzed data that form the background of this paper and believe that it is fabricated.  We call for it to be retracted.**

We had access to the contents of the notebooks of the laboratory in which this work was performed at the New Jersey Medical School in Newark, NJ, as one of us, HZH, was a member of the research team in that laboratory.  Further, PDF replicas of all the notebooks covering the period from 1995 to 2003 were subpoenaed during discovery in a *qui tam* law suit in which one of us, HZH, was the plaintiff and the other, JHP, was an expert witness.  We also examined certain additional data from 1992 that were produced during one of the depositions.  We are certain that our analysis applies to experiments reported in the *Micron* paper because the number of experiments that we found correspond to the number of experiments stipulated in the paper (except that 4 100% experiments were stipulated while we found 6 potential candidates) and the dates of the experiments precede the publication date of the paper.

We examined data sets that included two types of numerical data: 1) cell count numbers that were copied from the LED display of a Coulter ZM particle counter and 2) colony count numbers that were obtained by marking the bottoms of tissue culture dishes containing stained colonies of tissue culture cells and entered by hand into data sheets.  Most of the counts of both colonies and Coulters were performed in triplicate. Experimental results reported in the paper are based primarily on colony counts, but Coulter counts serve to verify and adjust the survival values.  Protocols of several pertinent experiments are appended.  Raw data of all of the counts we believe pertain to the questioned paper are also appended.

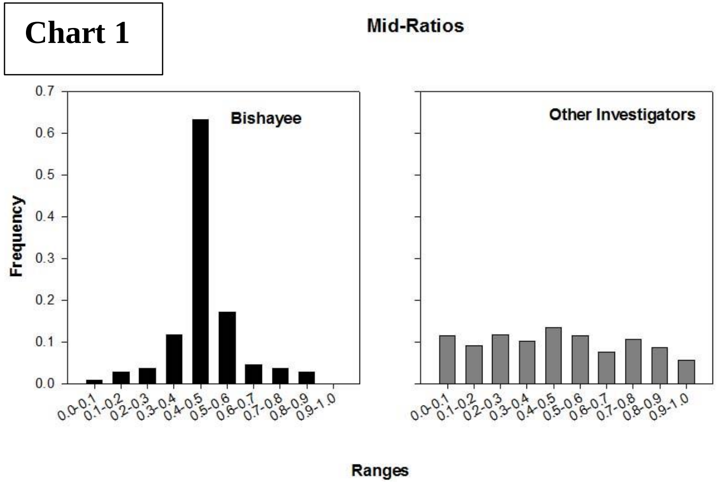
All of the data sets in which anomalous patterns appeared were from one investigator, Anupam Bishayee, who was a Research Teaching Specialist in the laboratory.  For control purposes we examined colony count and Coulter count data sets produced by 9 other investigators in the same laboratory as well as colony counts from 1 investigator in an independent lab and Coulter counts from 2 investigators in 2 independent labs. The control data sets we reviewed included 621 colony count triples and 946 Coulter count triples.  The control count data were all produced using methods identical to Bishayee's; using them we were able to: 1) verify our belief that the suspect patterns in Bishayee's data were not ordinarily present in presumed legitimate lab data; and 2) validate the applicability of the probability models we used to assay the likelihood that these patterns might have occurred by chance.

The three patterns that raise questions about the legitimacy of the Bishayee data are: 1) an unusually large percentage of the triples in his colony count data sets include the actual rounded average of the triple as an element; 2) the non-significant terminal digits of his Coulter count data do not appear to come from a uniform distribution as would ordinarily be expected; and 3) an improbably large percentage of terminal digit pairs of Coulter counts are identical. We discuss these three patterns in more detail below. We focus on data that we found in the discovery materials that pertain to *Micron* Figure 2.

**Pattern 1) An unusually large percentage of Bishayee's colony count triples, but not of the counts of others, include their rounded average as an element in those same triples**

**Mid-Ratios:** In reviewing Bishayee's colony count data (included in the Appendix) we noticed that a seemingly unusually large percentage of data triples included a value that closely approximated the triple's mean. In these experiments the means of the triples are effectively the key values that are to be associated with the corresponding treatments in subsequent analyses and are reflected as data points in the Figures in the paper. An investigator wishing to guide the results would need to construct data values for each triple such that its mean is consistent with the anticipated results. The quickest and easiest way to construct such a triple is to record the desired mean (or a close approximation) as one of the three count values and then, using two roughly equal constants, record the desired mean less the first constant and the desired mean plus the second constant as the two other count values of the triple. Such triples would, perforce, contain a value that is close to their mean.

**Chart 1**



In our first pass in trying to determine whether the frequent occurrence of such data triples was indeed unusual, we calculated a quantity that we refer to as the mid-ratio of each triple by sorting the numbers in each triple in ascending order and dividing the difference between the middle number and the smallest number by the difference between the largest number and the smallest number. If we use the letters a, b, c to represent the three values in a triple in ascending order then the mid-ratio $m = (b-a)/(c-a)$. When the gap, the difference between the largest element of a triple and the smallest (i.e. $c-a$) is 10 or more the mid-ratio of a triple will be near 0.5 on exactly those occasions that that triple contains an element whose value is close to its average.

We calculated the mid-ratios for the 111 data triples with gaps of 10 or more among the 136 sets of triplicate colony counts that Bishayee recorded for his 16 experiments for the *Micron* paper and did the same for the 572 such triples recorded for 62 experiments performed by 9 other investigators in the same laboratory and generated relative frequency histograms for each. The results shown in Chart 1 highlight a truly unusual prominence of triples that include values near their means in Bishayee's data set.

**Some triples actually contain their rounded mean:** Bishayee's colony data sets do not merely include a high percentage of triples with mid-ratios near 0.5, they actually contain what appeared to us to be unusually large numbers of triples that actually contained their rounded average as one of their three elements (see Appendix). We were able to carry the investigation further by developing a statistical model[1] to calculate the probabilities that individual triples actually include their own rounded average. Each triple consists of 3 independent counts and the model assumes that the three counts in each individual triple are the values generated by identical Poisson random variables.

The probability that a given triple contains its mean varies with the expected value (λ) of the Poisson variables that generate it. The Poisson variables of each individual triple have the same expected value, but those from different triples will have different expected values because of the variation in the numbers of cells initially plated and the variation in the effects of different levels of radiation. We do not know these expected values but can use the mean value of each triple to estimate the common expected value of the Poisson variables, and we then use that to estimate the probability that a similarly generated triple would have actually contained its mean. This allows us to construct estimates for the expectation and standard deviation of the number of mean containing triples that would appear by chance in a given collection of triples, and to construct an estimate that a given set of n triples, had it been generated honestly, would have contained k or more triples that contain their rounded means.

We validated the model by running it against the data sets of colony triples that we obtained from the nine other investigators in the same lab and from one outside investigator. The results are shown in Table 1. In both instances the actual number of mean containing triples was moderately less than the expected number according to our model. Certainly no cause for concern.

| **Table 1** | | **Colonies** | ***N*** **Qualifying Triples** | **K # w Mean** | **# Expected** | | ***probability ≥K*** |
|---|---|---|---|---|---|---|---|
| **9 Other Investigators*** | | | 572 | 109 | 111.80 | | *0.633* |
| **1 Outside Investigator** | | | 49 | 3 | 7.90 | | *0.989* |
| *62 Experiments from 6/30/92 to 11/27/02 | | | | | | | |

We then used this model to determine whether the numbers of mean containing triples in each of the Bishayee colony count data sets used in creating *Micron* Figure 2 should be a matter of concern. The results are shown in Table 2. Out of Bishayee's total of 133 complete triples with gaps of two or more, 76 included their rounded mean as one of their three values. According to

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[1] In preparation for publication – preprint available on request

our model, the probability, 2.95 x $10^{-25}$, is miniscule that there might be 76 or more such triples with rounded means among the 136 he recorded.

Looking at the results on an experiment by experiment basis provides further cause for concern. In eleven of the sixteen individual experiments the numbers of mean containing triples is found to be significantly higher than might be expected by chance at the 0.05 level, in eight, the results are significant at the 0.01 level, and in six at the 0.001 level. We believe this provides strong evidence of the likelihood that the results were guided by a preconceived notion of what the survival curves should be and the data were manipulated to conform to that notion. We emphasize that any conclusions based on these data cannot be reliable. We believe that we are presenting very strong statistical evidence for data fabrication, unless Drs Howell and Bishayee can come up with some other logical explanation for them.

| **TABLE 2** | **ID** | **Date** | ***N*** **Qualifying Triples*** | ***K*** **# w Mean** | **# Expected** | **Std Dev** | ***probability ≥ K*** |
|---|---|---|---|---|---|---|---|
| ***Micron*** **Figure 2** | **100%** | 8/26/1999 | 9 | 6 | 1.80 | 1.19 | ***3.04E-03*** |
| | | 8/30/1999 | 10 | 7 | 1.95 | 1.22 | ***4.92E-04*** |
| | | 6/12/2000 | 8 | 1 | 2.12 | 1.25 | *0.916* |
| | | 7/31/2000 | 7 | 5 | 1.30 | 1.02 | ***2.85E-03*** |
| | | 10/2/2000 | 7 | 4 | 1.51 | 1.06 | *0.169* |
| | | 10/5/2000 | 7 | 3 | 1.59 | 1.08 | *0.0450* |
| | **All** | | 48 | 26 | 10.27 | 2.79 | ***4.27E-07*** |
| | | | | | | | |
| | **50%** | 9/23/1999 | 10 | 9 | 1.69 | 1.17 | ***5.64E-07*** |
| | | 9/27/1999 | 10 | 7 | 1.76 | 1.18 | ***2.67E-04*** |
| | | 6/22/2000 | 10 | 4 | 1.68 | 1.16 | *0.0675* |
| | | 7/13/2000 | 7 | 2 | 1.10 | 0.95 | *0.304* |
| | | 7/20/2000 | 7 | 4 | 1.41 | 1.04 | *0.0309* |
| | | 8/10/2000 | 7 | 5 | 1.44 | 1.05 | ***4.25E-03*** |
| | **All** | | 51 | 31 | 9.09 | 2.68 | ***3.30E-12*** |
| | | | | | | | |
| | **10%** | 10/11/1999 | 10 | 7 | 1.47 | 1.11 | ***1.05E-04*** |
| | | 6/19/2000 | 10 | 5 | 1.71 | 1.18 | *0.016* |
| | | 8/3/2000 | 7 | 2 | 1.08 | 0.95 | *0.297* |
| | | 8/7/2000 | 7 | 5 | 1.09 | 0.95 | ***1.35E-03*** |
| | **All** | | 34 | 19 | 5.35 | 2.11 | ***7.15E-08*** |
| **Grand Total** ***Micron*** **Figure 2** | | | 133 | 76 | 24.71 | 4.40 | ***2.95E-25*** |

***** For qualifying gaps (c-a) ≥ 2

**Pattern 2) Terminal digits of Bishayee's Coulter counts, but not the Coulter counts of others, do not appear to come from a uniform distribution:** In investigations in which the terminal digits of data are immaterial and relatively insignificant, it is reasonable to expect these digits to be essentially random, hence to behave as if drawn from a uniform distribution. The Coulter count data for these experiments are digital readouts of 3 independent counts of cells drawn from a single cell suspension. These cell counts are in the 400 to 700 range (see Appendix). We assume that their rightmost digits are not controlled in any way by the investigator, hence will be effectively random. The recorded counts are based on readouts from a digital device, so their randomness is unlikely to be affected by investigator preferences for particular digits[2].

**Table 3 Coulter Digit Analysis**

| ***Micron* Figure 2** | | | **Terminal Digit** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **ID** | **Date** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **Total** | ***Chi Sq p*** |
| | **100%** | 8/26/1999 | 3 | 4 | 5 | 1 | 0 | 4 | 2 | 3 | 1 | 7 | 30 | *0.148* |
| | | 8/30/1999 | 0 | 3 | 5 | 4 | 1 | 3 | 1 | 3 | 1 | 9 | 30 | *0.014* |
| | | 6/12/2000 | 1 | 6 | 8 | 2 | 0 | 4 | 1 | 2 | 0 | 6 | 30 | ***4.30E-03*** |
| | | 7/31/2000 | 0 | 0 | 3 | 1 | 1 | 9 | 0 | 1 | 1 | 5 | 21 | ***6.30E-04*** |
| | | 10/2/2000 | 2 | 2 | 1 | 6 | 0 | 1 | 2 | 2 | 0 | 5 | 21 | *0.113* |
| | | 10/5/2000 | 2 | 5 | 6 | 2 | 0 | 1 | 0 | 1 | 0 | 4 | 21 | *0.045* |
| | **All** | | 8 | 20 | 28 | 16 | 2 | 22 | 6 | 12 | 3 | 36 | 153 | ***2.22E-12*** |
| | | | | | | | | | | | | | | |
| | **50%** | 9/23/1999 | 1 | 6 | 3 | 2 | 0 | 8 | 1 | 1 | 1 | 7 | 30 | ***2.62E-03*** |
| | | 9/27/1999 | 1 | 4 | 9 | 0 | 0 | 4 | 4 | 2 | 0 | 6 | 30 | ***1.59E-03*** |
| | | 6/22/2000 | 1 | 5 | 8 | 2 | 0 | 2 | 0 | 2 | 1 | 9 | 30 | ***2.59E-04*** |
| | | 7/13/2000 | 3 | 2 | 1 | 3 | 1 | 1 | 4 | 1 | 0 | 5 | 21 | *0.366* |
| | | 7/20/2000 | 0 | 4 | 5 | 1 | 0 | 4 | 0 | 1 | 0 | 6 | 21 | *0.017* |
| | | 8/10/2000 | 0 | 7 | 4 | 0 | 1 | 1 | 1 | 2 | 0 | 5 | 21 | *0.013* |
| | **All** | | 6 | 28 | 30 | 8 | 2 | 20 | 10 | 9 | 2 | 38 | 153 | ***8.10E-17*** |
| | | | | | | | | | | | | | | |
| | **10%** | 10/11/1999 | 1 | 4 | 9 | 2 | 0 | 4 | 0 | 2 | 0 | 8 | 30 | ***1.99E-04*** |
| | | 6/19/2000 | 1 | 6 | 5 | 1 | 0 | 4 | 3 | 1 | 2 | 7 | 30 | *0.044* |
| | | 8/3/2000 | 0 | 4 | 4 | 1 | 0 | 1 | 2 | 1 | 1 | 7 | 21 | *0.036* |
| | | 8/7/2000 | 1 | 4 | 2 | 2 | 1 | 0 | 0 | 4 | 1 | 6 | 21 | *0.113* |
| | **All** | | 3 | 18 | 20 | 6 | 1 | 9 | 5 | 8 | 4 | 28 | 102 | ***2.88E-11*** |
| | | **Total** | 17 | 66 | 78 | 30 | 5 | 51 | 21 | 29 | 9 | 102 | 408 | **1.16E-43** |
| | | **Percent** | **3.92** | **16.18** | **19.12** | **7.60** | **1.23** | **12.50** | **5.15** | **7.11** | **2.45** | **24.75** | | |
| | | | | | | | | | | | | | | |
| **9 Other Investigators** | | | 249 | 294 | 276 | 244 | 296 | 270 | 284 | 258 | 306 | 282 | 2759 | ***0.126*** |
| | | **Percent** | **9.03** | **10.66** | **10.00** | **8.84** | **10.73** | **9.79** | **10.29** | **9.35** | **11.09** | **10.22** | | |
| | | | | | | | | | | | | | | |
| **Outside Investigators** | | **lab 1** | 28 | 34 | 29 | 24 | 27 | 36 | 44 | 33 | 26 | 33 | 314 | ***0.36*** |
| | | **lab 2** | 34 | 38 | 45 | 35 | 32 | 42 | 31 | 35 | 35 | 33 | 360 | ***0.84*** |
| | | **Percent** | **9.20** | **10.68** | **10.98** | **8.75** | **8.75** | **11.57** | **11.13** | **10.09** | **9.05** | **9.79** | | |

As part of our investigation we processed Bishayee's Coulter count data sets as well as those from other investigators, creating frequency tables for the terminal digit values. The results are shown in Table 3. As can readily be seen, relative frequencies for the ten possible terminal digits are relatively flat for the data from other investigators, ranging from a low of 8.75% to a high of

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[2] Mosimann *et al.* (Mosimann, J. E., D. V. Wiseman, et al. (1995). "Data fabrication: Can people generate random digits?" Accountability in Research **4**: 31-55 and Mosimann, J. E., J. E. Dahlberg, et al. 2002). "Terminal digits and the examination of questioned data." Accountability in Research **9**: 75-92) use this test to show that humans are quite inept at producing randomized data.

11.57%. These frequencies vary widely in the set of 408 terminal digits from Bishayee's Coulter counts, varying from a low of 1.23% to a high of 24.75%. Applying the standard chi-squared goodness of fit test available in Excel to determine the probability of drawing a similarly varied set of 408 terminal digits from a uniform distribution we obtain a chi-squared probability of 1.16 x $10^{-43}$.

**Pattern 3) An improbably high percentage of Bishayee's Coulter counts, but not the Coulter counts of others, have equal terminal digits:** Under ordinary circumstances the probability that a Coulter count terminates in equal digits should be about 0.10, hence we would expect that roughly 10% of a collection of Coulter count data values would have equal terminal digits. The 2759 Coulter count values from the 9 other investigators in the same lab include 280 values with equal terminal digits or 10.1% the probability for which, using the statistical program R, is approximately 0.41. The 408 Coulter values that Bishayee recorded include 63 with equal terminal digits or 15.4%, a probability of 3.77 x $10^{-4}$ again determined using R. This probability is well below the canonical p of 0.05 for statistical significance (see Appendix).

We conclude that a major part of the representations of the data shown in the *Micron* paper are the result of fabrication and cannot be relied on. **We call for the paper to be retracted.**

Sincerely yours,

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**Appendix:**

Howell RW, Bishayee A. Bystander effects caused by nonuniform distributions of DNA-incorporated $^{125}$I. *Micron* 33: 127-133 (2002)
Spreadsheets:

Other Investigators Colony Analysis
Outside Investigator Colony Analysis
Bishayee Colony Analysis
Bishayee Coulter Analysis
Other Investigators Coulter Analysis

Bshayee Raw Data:

6 100% Experiments (+ 1 protocol)
6 50% Experiments (+ 1 protocol)
4 10% Experiments (+ 1 protocol)

NB: Bishayee's experiments had either 10 or 14 samples. In those with 14, we only analyzed 7 of 14 as the other 7 were exposed to lindane and we presume they would not have been included as data in the *Micron* paper